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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/724,524	11/27/2000	Leonard G. Presta	GENENT.33CP2C2	6863

20995 7590 10/23/2002

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EXAMINER
DAVIS, MINH TAM B

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 10/23/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No. 09/724,524	Applicant(s) PRESTA ET AL.	
	Examiner MINH-TAM DAVIS	Art Unit 1642	

-- The MAILING DATE of this c mmunication appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-12* is/are pending in the application.

4a) Of the above claim(s) *11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-10 and 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachm nt(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's election with traverse of group II, claims 6-12, a method for diagnosis of a pathological condition characterized by over-expression of trkB, a neurotrophin receptor, species neurodegenerative diseases, and competitive binding assay in Paper No. 9 is acknowledged. The traversal is on the ground(s) that group II and V should be examined together, since claim 6 has been amended to recite the "differential expression" of trkB neurotrophin receptor, which adequately covers both situations of over- and under-expression of trkB neurotrophin receptor. This is not found persuasive because the methods of groups II and V differ at least in method steps, reagents and/or dosages, and/or schedules used, response variables and criteria for success.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 6-10, 12, species neurodegenerative diseases, and competitive binding assay are examined in the instant application, wherein claims 6-10, 12 are examined only to the extent of a method for diagnosis of a pathological condition characterized by over-expression of trkB, a neurotrophin receptor. Claim 11, drawn to a non-elected species is withdrawn from consideration.

PRIORITY DATE

The Examiner has established a priority date Feb/20/2002, the date of the submission of claims 6-12 for the instantly claimed application serial number 09/724524 as the application to which priority is claimed does not recite the limitation of a method for the diagnosis of a pathological condition characterized by the over-expression or

under-expression of trkB neurotrophin receptor. Applicant is invited to submit evidence pointing to the serial number, page and line where support can be found establishing an earlier priority date.

Claim Rejections - 35 USC § 112 FIRST PARAGRAPH, NEW MATTER

Claims 6-10, 12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 6-10, 12 are drawn to a method for diagnosis of a pathological condition characterized by over-expression of trkB, a neurotrophin receptor, comprising testing the presence of an antibody specific for said neurotrophin receptor.

The specification does not disclose a method for diagnosis of a pathological condition characterized by over-expression of trkB, a neurotrophin receptor, comprising testing the presence of an antibody specific for said neurotrophin receptor.

Claim Rejections - 35 USC § 112, SECOND PARAGRAPH

Claims 6-10, 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claims 6-10, 12 are indefinite for the use of the language "differential expression" in claim 6, which could be both "increase and decrease" of the expression of TrkB. It is

not clear how a particular disease could be diagnosized by both an "increase and decrease" of the expression of TrkB, which are opposite from each other.

2. Claims 6-10, 12 are indefinite because claim 6 misses an important step. It is not clear how the presence of the antibody in complex with trkB as compared to age-matched normal control would result in the diagnosis of the pathological condition.

3. Claims 6-10, 12 are indefinite for the use of the language "characterized" in claim 6. It is not clear how the pathological condition is characterized.

Claim Rejections - 35 USC § 112 FIRST PARAGRAPH, SCOPE

Claims 6-10, 12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for diagnosis of Alzheimer's disease, or Huntington's disease, comprising detecting the expression of full length trkB in the hippocampus, and the truncated trkB in senile plaques in hippocampus and temporal lobe , wherein the presence of full length trkB in the hippocampus and the presence of truncated trkB in senile plaques in hippocampus and temporal lobe indicates Alzheimer's disease, and wherein the presence of truncated trkB in senile plaques only indicates the presence of Huntington's disease, does not reasonably provide enablement for diagnosis of any pathological conditions or any neurodegenerative diseases, comprising detecting the presence of any forms of trkB in any tissues. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 6-10, 12 are drawn to a method for diagnosis of a pathological condition characterized by over-expression of trkB, a neurotrophin receptor, comprising testing the presence of an antibody specific for said neurotrophin receptor in a biological sample. The pathological condition is neurodegenerative diseases. Said method comprises competitive binding assays. Said sample is tissue.

The claims encompass a method for diagnosis of any pathological condition characterized by over-expression of trkB, or of any is neurodegenerative disease, comprising detecting overexpression of any forms of trkB, either full length or truncated, in any type of tissues.

The specification discloses detection of the full length 8.1 kb transcript of trkB, and at least one truncated 6.9 kb transcript of trkB in human or two truncated forms of trkB in rodents, wherein trkB mRNAs are in greater abundance in the brain, besides the presence of the 8.1kb transcript in kidney, skeletal muscle and pancreas, and of the truncated form in heart, spleen and ovary (page 101, second paragraph, page 104, figure 6 and figure 6 legend on pages 12-13).

There is no disclosure in the specification of which pathological conditions, nor which neurodegenerative diseases that have over-expression of trkB proteins.

One cannot extrapolate the teaching of the specification to the scope of the claims. Without any relevant disclosure in the specification concerning which pathological conditions are characterized by differential expression of trkB, one cannot extrapolate to a method of diagnosis of any pathological condition characterized by the over-expression of trkB. Soontornniyomkij et al, 1999, Acta neuropathologica 98(4):

345-8, however, teach that expression of trkB proteins is characteristic of particular disease processes (abstract) .

Further, it is well known in the art that not any neurodegenerative disease over-expresses trkB proteins. Conner, B, et al, 1996, Mol Brain Res, 42: 1-17, teach that in contrast to Alzheimer's disease, no alteration in trkB full length or truncated proteins is found in the hippocampal formation in Downs syndrome (page 8, second column, section 3.1.4).

Thus without any relevant disclosure in the specification, and in view of the teaching in the art, it is unpredictable that trkB is overexpressed in any pathological condition or any neurodegenerative disease.

In addition, one would not expect to detect neurodegenerative diseases in any tissues, such as kidney, skeletal muscle and pancreas because there is no indication that overexpression of trkB in these tissues, which are not neural or brain tissues, is correlated with neurodegenerative diseases. Further, not any cells or any regions of the brain expresses trkB proteins, because there is differential expression of a trkB protein in different types of cells in the brain. Soontornniyomkij et al, *supra*, teach that while a catalytic trkB protein (full length trkB) is not found in glia in patients with Alzheimer's disease, it is present in neuronal perikarya in the neocortex and hippocampus of said patient.

Moreover, since trkB is expressed at least in two different forms, it is not clear that the claimed detection is based on which form of trkB , because it is not neccessarily that the splice variants of expressed in the same pattern as the wild type parent

wild type parent sequence. For example, Conner et al, *supra*, teach that full length trkB is found the hippocampus in patients with Alzheimer's disease, but not in hippocampi of either normal age-matched individual or patients with Huntington's disease, and that truncated trkB is found in senile plaques in hippocampus and temporal lobe in both patients with Alzheimer's disease and Huntington's disease, but not in normal brains of aged-matched individuals (page 8, item 3.1.2).

In view of the above, it would have been undue experimentation for one of skill in the art to practice the claimed invention as broadly as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 6-7, 9-10, 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Conner et al, 1996, *supra*.

Claims 6-7, 9-10, 12 are drawn to a method for diagnosis of a pathological condition characterized by over-expression of trkB, a neurotrophin receptor, comprising testing the presence of an antibody specific for said neurotrophin receptor in a biological

sample. The pathological condition is neurodegenerative diseases. Said sample is tissue of a human.

Conner et al, teach that using an antibody specific for trkB in the carboxy terminal domain (p.2, second column, second paragraph) and immunohistochemical techniques (page 2, second column, last pargraph, bridging page 3), full length trkB is found the hippocampus in patients with Alzheimer's disease, but not in hippocampi of either normal age-matched individual or patients with Huntington's disease, and that truncated trkB is found in senile plaques in hippocampus and temporal lobe in both patients with Alzheimer's disease and Huntington's disease, but not in normal brains of aged-matched individuals (page 8, item 3.1.2).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 6, 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Conner et al, *supra*.

Claims 6, 8 are drawn to a method for diagnosis of a pathological condition characterized by over-expression of trkB, a neurotrophin receptor, comprising testing

the presence of an antibody specific for said neurotrophin receptor in a biological sample. Said method comprises competitive binding assays.

The teaching of Conner et al has been set forth.

Conner et al however do not teach competitive binding assays.

The Examiner takes note that competitive binding assays are well known in the art for detection of various compounds, using antibodies.

It would have been *prima facia* obvious to a person of ordinary skill in the art at the time the invention was made to replace the immunohistochemical method taught by Conner et al with competitive binding assays for detection of neurodegenerative diseases, as taught by Conner et al, because they are all well known methods for detection the presence of compounds using antibodies, and would provide the same results.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

MINH TAM DAVIS

October 9, 2002

SUSAN UNGAR, PH.D
PRIMARY EXAMINER